Structural Enigmas Concerning Transcription and Replication of Rabies Virus

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Rabies virus is an RNA virus that has a non-segmented single stranded RNA genome that has the opposite sense of that of mRNA. This implies that the first step in the infection process is transcription of the viral genomic RNA into mRNA. For this process the virus carries an elaborated structure that is injected into the cytoplasm of the infected cell; the nucleocapsid. This helical structure contains the viral RNA that is bound to multiple copies of the viral nucleoprotein (N) with a stoichiometry of 1 N-protomer to 9 ribonucleotides. The viral RNA-dependent RNA polymerase complex is attached to this N-RNA structure. The polymerase is a hetero-oligomer consisting of the phosphoprotein (P) and the Large (L) protein that carries the polymerase activity. The helical N-RNA complex is the real target for the polymerase complex as it is inactive on naked RNA.

We were able to solve the structure of a recombinant form of the N-RNA complex in which it can clearly be seen how N binds to the sugar-phosphate backbone of the RNA [1]. However, the N-protomers totally surrounded the RNA and in such a structure the polymerase does not have access to the RNA for its transcription and replication activities. Therefore, we hypothesized that when the phosphoprotein of the polymerase complex binds to the N-RNA, a conformational change in N may take place such that the RNA is locally liberated.

We will show recent data on the structure of the phosphoprotein from rabies virus and on titrations of the intact protein and its N-RNA binding domain to the recombinant N-RNA and to viral N-RNA complexes. Electron micrographs of such complexes and of complexes of a related virus, Vesicular Stomatitis Virus, indeed show important conformational changes in the N-RNA when the phosphoprotein binds to it but we have not yet been able to analyse these changes at high resolution because of the flexibility of the helices.

References

[1] Albertini, A.A.V., Wernimont, A.K., Muziol, T., Ravelli, R.B.G., Clapier, C.R., Schoehn, G., Weissenhorn, W. and Ruigrok, R.W.H. Science **313**, 357-360, (2006)